INTERESTING SOLVENT AREA IN CRYSTAL STRUCTURES OF TWO NATURAL ERGOT ALKALOIDS

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The structures of ergotamine bis(benzene) solvate (**1**) and ergocristine bis(benzene) solvate (**2**) are reported. Both structures crystallise in the $P2_12_12_1$ space group with cell parameters: **1**, a = 14.2968(3) Å, b = 15.4700(2) Å, c = 17.8123(4) Å, and V = 3939.57(13) Å^3; **2**, a = 11.8358(2) Å, b = 17.6469(3) Å, c = 19.7125(3) Å, and V = 4117.25(12) Å^3. Unexpectedly, despite the chemical similarity, structures of **1** and **2** significantly differ not only in the unit cell parameters, but also in the packing. Whereas in **1** solvent cavities are separated, there is only one unusual continuous solvent area in **2** filled with benzene, forming independent three-dimensional structure.

Keywords: Ergotamine; Ergocristine; Ergot alkaloids; Indole alkaloids; Crystal structure; X-ray diffraction; Solvates.

The toxic effect of ergot is probably first mentioned around 600 BC, but epidemics of ergotism occurred also in a very recent history[1–3]. Toxic effects of natural ergopeptine alkaloids, particularly their vasoconstrictive action, are responsible for the epidemics of ergotism. Poisoning due to ergot alkaloids resulted in gangrene of the limbs and CNS disturbances, and ultimately in death. Later on, some ergot alkaloids were used for medicinal purposes, but due to their side effects facilitated by binding to various receptors[4], the use of other natural ergot alkaloids was nearly abandoned. Recently, however, semisynthetic ergopeptine derivatives have found an incommutable role in

the treatment of, e.g., migraine, cognitive deterioration, cerebrovascular and many other diseases[3,5].

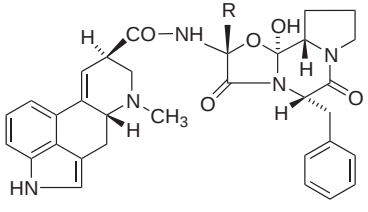
Whereas considerable attention has been devoted to the structure of various semisynthetic ergot derivatives, much less interest has been paid so far to the structures of original natural ergopeptines and to comparison of their conformations with new derivatives. Out of about 20 natural peptidic alkaloids, the structures of ergocristine acetone solvate[6], ergogaline hydrate[7], ergoladinine[8], ergocristam[6], and some 8-hydroxyergopeptines[9] were reported. The structure of ergotamine, the only ergopeptine alkaloid, which had found medicinal use in its unmodified form, was reported for its tartrate salt[10,11].

The aim of this work is to report the structure of two "old" natural ergopeptine alkaloids. Conformations of these two natural ergopeptine alkaloids are compared with related structures found in Cambridge Structural Database – ergotamine tartrate ethanol solvate (HICCUR)[9] and ergocristine acetone solvate (NUDWEO)[6] and also with their semisynthetic derivatives – dihydroergotamine mesylate monohydrate (HERGOM)[12], dihydroergocristine bis(dioxane) solvate (QABBUQ)[13], and dihydroergocristine mesylate monohydrate (ZIYGIX)[14].

EXPERIMENTAL

Preparation of Crystals

Single crystals of ergotamine bis(benzene) solvate (**1**) suitable for X-ray diffraction measurements were obtained by slow evaporation of an ergotamine (120 mg) solution in a mixture of acetone (20 ml) and benzene (100 ml). Colourless prism, m.p. 143 °C with decomposition (DSC). Single crystals of ergotamine bis(benzene) solvate (**2**) were prepared by slow evaporation of an ergocristine (255 mg) solution in benzene (7 ml). Colourless prism, m.p. 122 °C with decomposition (DSC).



1, R = CH_3; bis(benzene) solvate
2, R = $CH(CH_3)_2$; bis(benzene) solvate

X-ray Structure Analysis

The summary of crystallographic data and refinement parameters is given in Table I. Both structures were solved by direct methods and refined by full-matrix least squares. Hydrogen atoms were located from the expected geometry and Δρ maps in both cases and their positional and isotropic parameters were refined. The Flack's parameters were refined and their values were surprisingly in good agreement with known chiralities of the natural compounds (high e.s.d.'s due to Mo radiation used). Programs used for structure solutions,

TABLE I
Crystal data and structure refinement

Parameter	**1**	**2**
Chemical formula	$C_{45}H_{47}N_5O_5$	$C_{47}H_{51}N_5O_5$
Formula weight	737.9	766.0
Temperature, K	150	150
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	14.2968(3)	11.8358(2)
b, Å	15.4700(2)	17.6469(3)
c, Å	17.8123(4)	19.7125(3)
V, Å^3	3939.6(1)	4117.3(1)
Z	4	4
Density (calculated), mg m^{-3}	1.24	1.24
Absorption coefficient, mm^{-1}	0.082	0.081
Flack parameter	0.1 (6)	0.1 (7)
Diffractometer and radiation used, Å	Nonius Kappa CCD, 0.71073	Nonius Kappa CCD 0.71073
Scan technique	ψ and ω	ψ and ω
θ range for data collection, °	1.940–26.020	1.549–27.486
Reflections measured	24 747	22 550
Independent/observed reflections	7722/6644 [$I > 1.96\sigma(I)$]	9432/8145 [$I > 1.96\sigma(I)$]
Parameters refined	685	719
Goodness of fit on F^2	1.1041	1.0911
Final *R* indices [$I > 1.96\sigma(I)$]	*R1* = 0.0459, *wR2* = 0.0352	*R1* = 0.0427, *wR2* = 0.0383
R indicesall data	*R1* = 0.0583, *wR2* = 0.0407	*R1* = 0.0559, *wR2* = 0.0482

refinements, calculations and visualisations were: COLLECT [15], DENZO/SCALEPACK [16], SHELXS86 [17], CRYSTALS [18], PARST [19], PLATON [20] and ORTEP-3 [21]. CCDC 205936 (for **1**) and 205935 (for **2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

The structures of ergotamine bis(benzene) (**1**) and ergocristine bis(benzene) (**2**) solvates are depicted in Figs 1 and 2, respectively. Conformations of these new structures were compared with their conformations in related structures and also with those of some semisynthetic derivatives. For the puckering parameters of rings C, D, F, and G see Table II. Rings A, B, and E are planar in all the studied structures and thus are omitted in Table II. The conformations of the rings C and F are almost the same for all the studied structures – these rings have envelope conformations E_3 (for the ring C) and ^6E (for the ring F).

However, what is unusual with both structures **1** and **2** is their conformation of ring D. The "obligatory" presence of intramolecular hydrogen bond N3–H3···N2, stabilising ergopeptine conformation devoted as "CB" (or flap

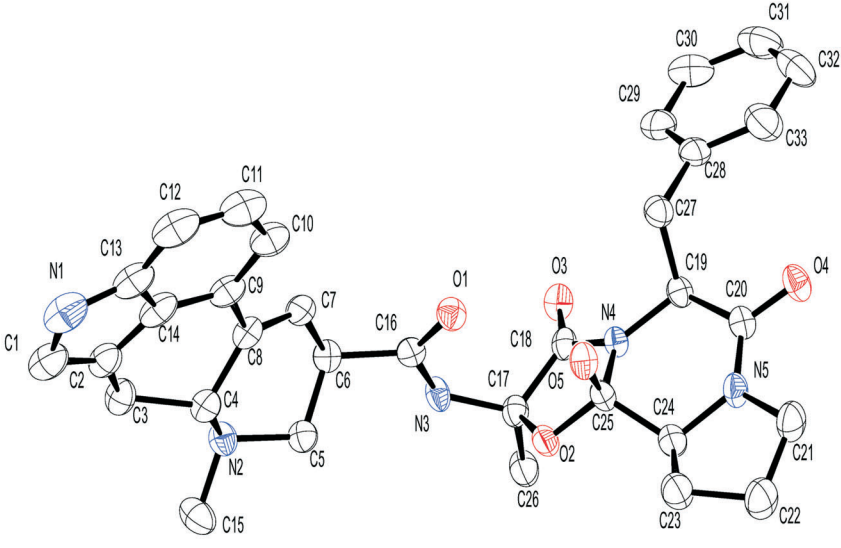


FIG. 1
ORTEP drawing of ergotamine bis(benzene) solvate with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen and solvent atoms were omitted for clarity

down, **II**)[22,23], was expected in all natural ergopeptine structures crystallised as free bases from non-polar solvent[23]. In fact, it was really formed only in the case of ergocristine acetone solvate[6] (Fig 3a). In ergocristine acetone solvate (NUDWEO), the ring D has the half-chair conformation $^{1}H_{6}$. In contrast, the conformations of the ring D lay between $^{6}H_{1}$ and ^{6}E for structures of **1** and **2** (closer to $^{6}H_{1}$) and for ergotamine tartrate ethanol solvate (HICCUR – closer to ^{6}E)[9]. This conformation is devoted as "*E*" (or flap up, **I**)[22,23]. In fact, the couple of ergocristine acetone solvate – ergocristine benzene solvate seems to be the first example describing the role of packing on conformation of D-ring in ergopeptines. There is only one possible conformation of ring D in dihydroergopeptines devoted as "DHE" ($^{4}C_{1}$) due to the missing 8,9-double bond. Accordingly, this conformation was observed with dihydroergotamine mesylate monohydrate (HERGOM), dihydroergocristine bis(dioxane) solvate (QABBUQ), and dihydroergocristine mesylate monohydrate (ZIYGIX).

In the tripeptide moiety, ring E is planar. Ring G forms an envelope conformation ^{4}E in all **1**, **2**, HICCUR, NUDWEO, and QABBUQ. In the structures of mesylates – HERGOM and ZIYGIX – ring G has conformation $^{4}T_{5}$. There are also interesting differences in some torsion angles, e.g., of phenylalanine in **1** (ergotamine, χ^{1}(N4–C19–C27–C28) = –136.4(2)°) and **2** (ergocristine, χ^{1}(N4–C19–C29–C30) = –56.5(2)°). A superposition of **1** and **2**

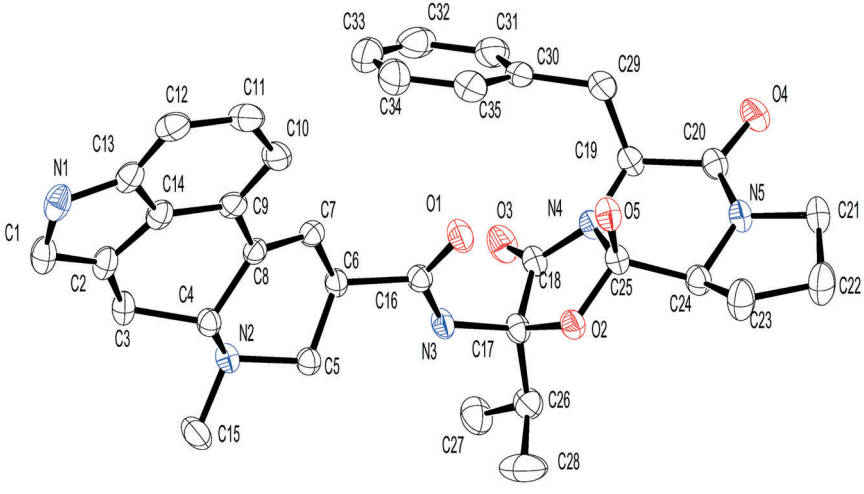


FIG. 2
ORTEP drawing of ergocristine bis(benzene) solvate with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen and solvent atoms were omitted for clarity

TABLE II
Conformations[a] of the rings C, D, F, and G in studied structures

Ring	Compound	φ, °	θ, °	*Q*, Å	Conformation
C	**1**	–71.5(3)	125.8(2)	0.453(2)	E_3
(C2–C3–C4–C8–C9–C14)	**2**	–64.7(2)	127.8(2)	0.424(2)	E_3
	HICCUR	–64	123	0.47	E_3
	HERGOM	–56	129	0.48	E_3
	NUDWEO	–60	127	0.48	E_3
	QABBUQ	–54	127	0.46	E_3
	ZIYGIX	–59	127	0.47	E_3
D	**1**	141.1(3)	127.2(2)	0.523(2)	${}^6H_1$–${}^6E$
(N2–C4–C8–C7–C6–C5)	**2**	138.8(2)	128.4(1)	0.544(1)	${}^6H_1$–${}^6E$
	HICCUR	131	129	0.53	${}^6E$–${}^6H_1$
	HERGOM	120	178	0.59	${}^4C_1$
	NUDWEO	–35	51	0.51	${}^1H_6$
	QABBUQ	–178	175	0.58	${}^4C_1$
	ZIYGIX	80	173	0.57	${}^4C_1$
F	**1**	109.8(2)	123.3(2)	0.465(2)	${}^6E$
(N4–C19–C20–N5–C24–C25)	**2**	117.9(2)	134.5(2)	0.424(1)	${}^6E$
	HICCUR	122	125	0.45	${}^6E$
	HERGOM	122	122	0.50	${}^6E$
	NUDWEO	124	127	0.44	${}^6E$
	QABBUQ	119	131	0.44	${}^6E$
	ZIYGIX	120	121	0.46	${}^6E$
G	**1**	–78.3(3)	–	0.383(3)	${}^4E$
(N5–C21–C22–C23–C24)	**2**	–73.1(3)	–	0.364(2)	${}^4E$
	HICCUR	–74	–	0.40	${}^4E$
	HERGOM	–53	–	0.28	${}^4T_5$
	NUDWEO	–73	–	0.36	${}^4E$
	QABBUQ	–70	–	0.38	${}^4E$
	ZIYGIX	–62	–	0.30	${}^4T_5$

[a] Cremer and Pople puckering parameters[28].

based on the fit of rigid ergolene moieties, Fig. 3b, indicates also some differences between the molecular conformations of both alkaloids.

Crystal structures of **1** and **2** exhibit also quite different solvent areas (Figs 4a and 4b). The solvent accessible areas of the new structures were calculated by the program Platon[20]. In the case of **1**, there are two cavities of volume 605 Å^3 formed by two pockets connected by very narrow neck, each of them containing two independent molecules of benzene. The first one (denominated as C34–C39) forms a π···π stacking with the amide part of the diketopiperazine skeleton in distance of approximately 3.5 Å. Interestingly, such strong interaction among two amide dipoles with polarizable π electron system was already found, e.g., in folded form of cyclic dipeptides (diketopiperazines) containing an aromatic side chain, and it is also in agreement with interaction of amides with aromatic solvents[24]. In addition to the dipole–induced dipole interaction, the interaction may be further stabilised by dispersion forces acting between the polarisable π system of the aromatic ring and the polarisable π systems of two amide groups. Furthermore, there are also C–H···π interactions of the first benzene molecule with the indole skeletons of two neighbouring ergotamine molecules in a distance of approximately 3.5 Å. A weak hydrogen bond C38–H···N2 ($-x + 1/2$, $-z$, $y + 1/2$) with separation 2.45 Å and angle 172° was found. The second benzene molecule (devoted as C40–C45) appears simply filling the gap in packing, but the rich van der Waals surroundings should not be overlooked.

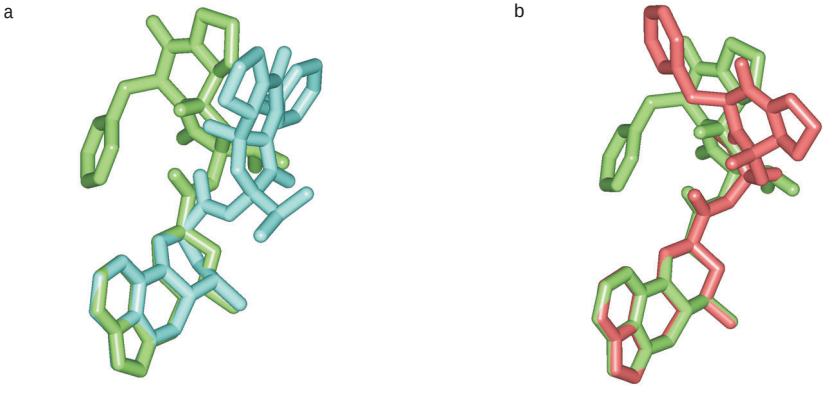


FIG. 3
a Superposition of ergocristine bis(benzene) solvate (green) and ergocristine acetone solvate (blue). b Superposition of ergocristine bis(benzene) solvate (green) and ergotamine bis(benzene) solvate (red)

The space arrangement of the benzene molecules in **2** is different from that found in **1**. The molecules fill continuous space having van der Waals contacts to each other and to the neighbouring ergocristine molecules. No clear π···π stacking or CH···π interactions were observed. There is only one continuous solvent area of the volume 1348 Å^3 in **2** filled with 8 molecules of benzene per the unit cell (Z = 4) thus forming an independent three-dimensional structure. However, the diameter and shape of cavities prevent the solvent "to flow" freely through the structure and thus the solvate is reasonably stable. This observation is also in agreement with considerably higher thermal stability of **1**. The considerably less dense packing seems to provide also the explanation of the lower density of **2** (1.236 g cm^{-3}) compared with **1** (1.244 g cm^{-3}). One weak hydrogen bond C42–H···O1 ($-x$, y + 1/2, $-z$ – 1/2) was characterised with separation 2.51 Å and angle 166°.

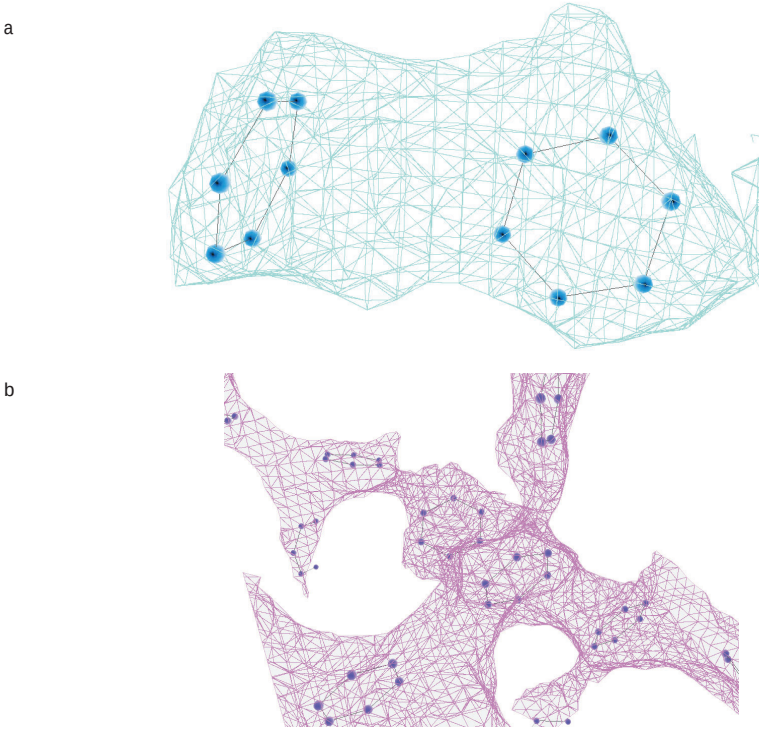


FIG. 4
a Solvent accessible area in structure of ergotamine bis(benzene) solvate at the 1.2 Å level (1.2 Å distance from the van der Waals sphere of the nearest atom). b Solvent accessible area in structure of ergocristine bis(benzene) solvate at the 1.2 Å level (1.2 Å distance from the van der Waals sphere of the nearest atom)

The ergolene moiety is usually considered as only one receptor site responsible for the activity of ergot derivatives. However, the fact that ergolene part is almost identical for all ergopeptine alkaloids cannot satisfactory explain their different pharmacological effects. It is noteworthy that diketopiperazines have been recently recognised as a highly specific class of receptors in combinatorial chemistry[25–27]. Thus the ability of ergopeptine alkaloids to provide such interaction could extend the understanding of differences in pharmacological activities of various ergot alkaloids.

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